Indeed, the memorandum describes the tobacco industry itself as a "segment of the pharmaceutical industry":[458]

> In a sense, *the tobacco industry may be thought of as being a specialized, highly ritualized and stylized segment of the pharmaceutical industry*. . . . Our Industry is then based upon design, manufacture and sale of attractive dosage forms of nicotine, and our Company's position in our Industry is determined by our ability to produce dosage forms of nicotine which have more overall value, tangible or intangible, to the consumer than those of our competitors. [459]

Finally, the memorandum recommends improvements in the delivery of nicotine to consumers. In the short term, the memorandum recommends reducing tar levels while maintaining nicotine levels in cigarettes:

> Our critics have lumped "tar" and nicotine together in their allegations about health hazards. . . . *An accompanying Research Planning Memorandum suggests an approach to reducing the amount of "tar" in cigarette smoke per unit of nicotine*. That is probably the most realistic approach in today's market for conventional cigarette products. [460]

In the long term, the memorandum recommends a "more futuristic approach":[461]

> *If our business is fundamentally that of supplying nicotine in useful dosage form, why is it really necessary that allegedly harmful "tar" accompany that nicotine*? There should be some simpler, "cleaner", more efficient and direct way to provide the desired nicotine dosage than the present system involving combustion of tobacco or even chewing of tobacco. . . . It should be possible to obtain pure nicotine by synthesis or from high-nicotine tobacco. *It should then be possible, using modifications of techniques developed by the pharmaceutical and other*

[458] *Id.* at 2.

[459] *Id.* (emphasis added).

[460] *Id.* at 6 (emphasis added).

[461] *Id.*

> *industries, to deliver that nicotine to the user in efficient, effective, attractive dosage form, accompanied by no "tar", gas phase, or other allegedly harmful substances.* The dosage form could incorporate various flavorants, enhancers, and like desirable additives, and would *be designed to deliver the minimum effective amount of nicotine at the desired release-rate to supply the "satisfaction" desired by the user.* Such a product would maximize the benefits derived from nicotine, minimize allegedly undesirable over-dosage side effects from nicotine, and eliminate exposure to other materials alleged to be harmful to the user. [462]

Evidence in the record indicates that RJR acted on both of these recommendations. *See* sections II.C.2.b.iii. and II.C.3.b., below.

Claude Teague's 1973 memorandum, entitled "Some Thoughts about New Brands of Cigarettes for the Youth Market," recommends that RJR develop "new brands tailored to the youth market."[463] According to the memorandum, one of the design features that should be tailored to the youth market is nicotine delivery. The memorandum reaffirms that the "nicotine effects" and the other physical effects of smoking are "highly desirable to the confirmed smoker."[464] For the "pre-smoker" or "learner," however, the memorandum states that the physical effects of smoking, including the effects of nicotine, are "largely unknown, unneeded, or actually quite unpleasant or awkward."[465] Consequently, the memorandum recommends that "the effort here should be to affect a compromise to minimize the undesirable effects while retaining these which later become

[462] *Id.* at 7 (emphasis added).

[463] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on Some Thoughts about New Brands of Cigarettes for the Youth Market* (Feb. 2, 1973), at 1. *See* AR (Vol. 531 Ref. 125).

[464] *Id.* at 4.

[465] *Id.* at 2, 4.

desirable."[466] With respect to nicotine, the memorandum recommends that "nicotine should be delivered at about 1.0-1.3 mg/cigarette, the minimum for confirmed smokers. The rate of absorption of nicotine should be kept low by holding pH down, probably below 6."[467]

Teague's analysis shows that, as at Philip Morris, scientists at RJR have long understood that nicotine has significant pharmacological effects on the body and is the "primary" reason people smoke. His analysis further shows that, like Philip Morris scientists, RJR scientists also expressly conceived of cigarettes as a drug delivery system.

ii. Other Statements and Research of RJR Scientists and Officials. The views in the Teague memoranda about the "crucial role" of the pharmacological effects of nicotine continued to be expressed within RJR in later years. In approximately 1977, for instance, RJR researchers told the RJR marketing department that "*[w]ithout any question, the desire to smoke is based on the effect of nicotine on the body*";[468] that "*a confirmed smoker attempts to get a certain desired level of nicotine*";[469] and that "[t]he nicotine in the blood acts upon the central nervous system and produces in the average smoker a sensation one could describe as either stimulating or relaxing."[470] According to the RJR researchers, while nicotine has a role in "mouth taste" and "mouth satisfaction,"

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[466] *Id.* at 4.

[467] *Id.*

[468] Senkus M (R. J. Reynolds Tobacco Co.), *Some Effects of Smoking* (1976/1977), at 4 (emphasis added). *See* AR (Vol. 700 Ref. 593).

[469] *Id.* at 5 (emphasis added).

[470] *Id.* at 3.

that is not nicotine's primary role; rather, "the ultimate satisfaction comes from the nicotine which is extracted . . . *in the lungs.*"[471]

In the late 1980's and early 1990's, moreover, RJR researchers conducted a series of experiments on how nicotine affects the brain. The published reports from these experiments revealed that 20 years after the Teague memoranda, RJR researchers continued to believe that: (1) nicotine has pharmacological effects on the brain; and (2) smokers smoke cigarettes primarily to obtain these pharmacological effects.

In a 1989 report entitled "Effects of Smoking/Nicotine on Anxiety, Heart Rate, and Lateralization of EEG During a Stressful Movie," RJR used an EEG to test its hypothesis that "nicotine and smoking help smokers to relax and cope with stress and negative affect" through "activation-reducing effects on the EEG."[472] The experiment's results supported RJR's hypothesis, indicating that nicotine produced the expected "anxiolytic" or anxiety-reducing effects in the brain:

> The present results support the view that the electrocortical effects of smoking are a function of environmental stress level, cigarette nicotine delivery, and cortical site. *They are also consistent with previous evidence that nicotine reduces anxiety and with our hypothesis that nicotine's anxiolytic properties are mediated by the right hemisphere.* Normal/high-nicotine delivery cigarettes, relative to low-nicotine control cigarettes, produced cortical activation (decreased alpha power) in both hemispheres during the no-stress control condition . . . but produced the opposite effect, decreased activation (increased alpha power), at the right parietal site during the three stressful movie scenes. [473]

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[471] *Id.* at 7-9 (emphasis added).

[472] Gilbert DG, Robinson JH, Chamberlin CL (R.J. Reynolds Tobacco Co.), *et al.*, Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie, *Psychophysiology* 1989;26(3):311-319, at 311. *See* AR (Vol. 14 Ref. 174-2).

[473] *Id.* at 316 (citation omitted) (emphasis added).

The 1989 study used the EEG to measure smokers' brain waves while they watched a film containing graphic images of industrial accidents. In a 1991 study entitled "Electroencephalographic Effects of Cigarette Smoking," RJR researchers measured the effects of smoking on brain waves under "levels of mental workload representative of those encountered in day-to-day living."[474] They found that the pharmacological effects of smoking are affected by how deeply the smoker inhaled. According to the report:

> In light inhaling smokers, . . . smoking was found to attenuate EEG activity in the delta, theta, and alpha frequency bands . . . . In deep inhaling smokers, smoking produced a symmetrical central midline increase in beta2 magnitude, *an EEG effect that . . . is associated with anxiety relief.*[475]

These results led the RJR researchers to propose that light inhalers and deep inhalers smoke to obtain different pharmacological effects from nicotine and that the effects produced in deep-inhalers were comparable to the effects of benzodiazepines, a class of addictive drugs used for anxiety relief. According to the report:

> The results of the present investigation indicate that *light inhaling . . . smokers may smoke primarily for purposes of mental activation and performance enhancement.* This does not appear to be the case for deeper inhaling . . . smokers. . . . An extensive literature suggests that increased beta2 activity may reflect the anxiolytic properties of the benzodiazepines independently of sedative effects. *Thus, an important smoking motive for deep inhaling smokers might be anxiety reduction.*[476]

A year later, the RJR researchers reported the results of a study designed to isolate the precise effects of nicotine on the brain. In this study, some smokers were given

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[474] Pritchard WS (R.J. Reynolds Tobacco Co.), Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490, at 486. *See* AR (Vol. 3 Ref. 23-2).

[475] *Id.* at 485 (emphasis added).

[476] *Id.* at 488 (citations omitted) (emphasis added).

regular "light" cigarettes to smoke while others were given experimental cigarettes with virtually no nicotine. The results from the EEG showed that the regular "light" cigarette produced "a significant increase in beta2 magnitude," an effect associated with anxiety relief, and "a significant decrease in delta magnitude," an effect associated with improved mental alertness.[477] According to the researchers, "*this indicates that the beneficial effects of smoking on cognitive performance . . . are a function of nicotine absorbed from cigarette smoke upon inhalation.*"[478]

In another report written in 1992, the RJR researchers addressed the question "why do people smoke?" The researchers reject the claim that people smoke to satisfy an addiction, but they do not reject the claim that people smoke to obtain other pharmacological effects from nicotine. To the contrary, as Claude Teague did 20 years earlier, they assert that the reason people smoke is precisely to obtain these pharmacological effects:

> We believe that a more reasonable hypothesis concerning why people smoke . . . is that *smokers use cigarettes primarily as a 'tool' or 'resource' that provides them with needed psychological benefits (increased mental alertness, anxiety reduction, coping with stress).*[479]

In its comments, RJR asserts that nicotine is important in cigarettes because "nicotine plays an important role in the taste and flavor of cigarette smoke."[480] The

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[477] Robinson JH, Pritchard WS, Davis RA (R.J. Reynolds Tobacco Co.), Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472, at 469. *See* AR (Vol. 11 Ref. 129-3).

[478] *Id.* at 471 (emphasis added).

[479] Robinson J, Pritchard W (R.J. Reynolds Tobacco Co.), The role of nicotine in tobacco use, *Psychopharmacology* 1992;108:397-407, at 398 (emphasis added). *See* AR (Vol. 34 Ref. 589).

[480] R.J. Reynolds Tobacco Co., Comment (Jan. 2, 1996), at 50. *See* AR (Vol. 519 Ref. 103).

history of RJR's research does not support the company's public position, however. If nicotine were important because of its role in taste, FDA would expect to find that RJR's research would focus on nicotine's impact on taste. The administrative record, however, contains virtually no RJR research demonstrating or investigating nicotine's influence on taste.[481] In contrast, RJR has extensively investigated the pharmacological impacts of nicotine. In total, the administrative record before FDA contains more than 20 studies published or funded by RJR on the effects of nicotine on the body.[482] The actual number

[481] There is little scientific support for the proposition that nicotine has an important role in cigarette taste. The four studies cited by RJR are all discussed in section II.B.2.c, above. Only one of the studies relied upon by RJR was actually conducted by RJR. This limited investigation by RJR into nicotine's role in taste was presented *after FDA's investigation had commenced.* Pritchard, WS, Robinson, JH, *The Sensory Role of Nicotine in Cigarette "Taste," Smoking Satisfaction and Desire to Smoke*, presented at the International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II (Montreal: Jul. 21-24, 1994). *See* AR (Vol. 519 Ref. 103, vol. II). As discussed in section II.B.2.c., above, RJR researchers conceded that the study was unable to distinguish the importance of any sensory aspects of nicotine from its pharmacological effects.

[482] Bjercke RJ, Langone JJ, Anti-idiotypic antibody probes of neuronal nicotinic receptors, *Biochem Biophys Res Commun* 1989;162(3):1085-1092. *See* AR (Vol. 46 Ref. 53).

Brazell MP, Mitchell SN, Gray JA, Effect of acute administration of nicotine on in vivo release of noradrenaline in the hippocampus of freely moving rats: a dose-response and antagonist study, *Neuropharmacology* 1991;30(8):823-833. *See* AR (Vol. 46 Ref. 58).

Byrd GD, Chang KM, Greene JM, *et al.*, Evidence for urinary excretion of glucuronide conjugates of nicotine, cotinine, and trans-3'-hydroxycotinine in smokers, *Drug Metab Dispos Biol Fate Chem* 1992;20(2):192-197. *See* AR (Vol. 120 Ref. 1131).

Caldwell WS, Green JM, Byrd GD, *et al.*, Characterization of the glucuronide conjugate of cotinine: a previously unidentified major metabolize of nicotine in smokers' urine, *Chem Res Toxicol* 1992;5(2):280-285. *See* AR (Vol. 46 Ref. 62).

Caldwell WS, Greene JM, Dobson GP, *et al.*, Intragastric nitrosation of nicotine is not a significant contributor to nitrosamine exposure, *Ann NY Acad Sci* 1993;686:213-227. *See* AR (Vol. 128 Ref. 1388).

Collins AC, Bhat RV, Pauly JR, *et al.*, Modulation of nicotine receptors by chronic exposure to nicotinic agonists and antagonists, in *The Biology of Nicotine Dependence*, eds. Bock G, Marsh J (CIBA Foundation Symposium 152, 1990), at 68-82. *See* AR (Vol. 47 Ref. 71).

deBethizy JD, Borgerding MF, Doolittle DJ, Chemical and biological studies of a cigarette that heats rather than burns tobacco, *J Clin Pharmacol* 1990;30(8):755-763. *See* AR (Vol. 47 Ref. 78).

deBethizy JD, Robinson JH, Davis RA, *et al.*, Absorption of nicotine from a cigarette that does not burn tobacco, *Pharmacology* 1988;37(5):328-332. *See* AR (Vol. 47 Ref. 79).

Gilbert DG, Robinson JH, Chamberlin CL, *et al.*, Effects of smoking/nicotine on anxiety, heart rate, and lateralization of EEG during a stressful movie, *Psychophysiology* 1989;26(3):311-319. *See* AR (Vol. 14 Ref. 174-2).

Hammond DK, Bjercke R.J, Langone JJ, *et al.*, Metabolism of nicotine by rat liver cytochromes P-450, Assessment utilizing monoclonal antibodies to nicotine and cotinine, *Drug Metab Dispos Biol Fate Chem* 1991;19(4):804-808. *See* AR (Vol. 48 Ref. 110).

Kyerematen GA, Morgan ML, Chattopadhyay B, *et al.*, Disposition of nicotine and eight metabolites in smokers and nonsmokers, *Clin Pharmacol Ther* 1990;48(6):641-651. *See* AR (Vol. 49 Ref. 146).

Kyerematen GA, Taylor LH, deBethizy JD, *et al.*, Pharmacokinetics of nicotine and 12 metabolites in the rat, Application of a new radiometric high performance liquid chromatography assay, *Drug Metab Dispos Biol Fate Chem* 1988;16(1):125-129. *See* AR (Vol. 49 Ref. 145).

Lippiello PM, Femandes KG, The binding of L-[3H]nicotine to a single class of high affinity sites in rat brain membranes, *Mol Pharmacol* 1986;29(5):448-454. *See* AR (Vol. 55 Ref. 165).

Lippiello PM, Mencherif M, Prince RJ, The role of desensitization in CNS nicotinic receptor function, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems* 1994, S11. *See* AR (Vol. 55 Ref. 166).

Lippiello PM, Sears SB, Femandes KG, Kinetics and mechanism of L-[3H]nicotine binding to putative high affinity receptor sites in rat brain, *Mol Pharmacol* 1987;31(4):392-400. *See* AR (Vol. 55 Ref. 162).

Marks MJ, Grady SR, Collins AC, Downregulation of nicotinic receptor function after chronic nicotine infusion, *J Pharmacol Exp Ther* 1993;266(3):1268-1276. *See* AR (Vol. 55 Ref. 176).

Mitchell SN, Brazell MP, Joseph MH, *et al.*, Regionally specific effects of acute and chronic nicotine on rates of catecholamine and 5-hydroxytxyptamine synthesis in rat brain, *Eur J Pharmacol* 1989;167(3):311-322. *See* AR (Vol. 57 Ref. 200).

Mitchell SN, Brazell MP, Schugens MM, *et al.*, Nicotine-induced catecholamine synthesis after lesions to the dorsal or ventral noradrenergic bundle, *European Journal of Pharmacology* 1990;179(3):383-391. *See* AR (Vol. 57 Ref. 197).

Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490. *See* AR (Vol. 3 Ref. 23-2).

Pritchard WS, Gilbert DG, Duke DW, Flexible effects of quantified cigarette smoke delivery on EEG dimensional complexity, *Psychopharmacology* 1993;113:95-102. *See* AR (Vol. 3 Ref. 23-1).

Pritchard WS, Robinson JH, Guy TD, Enhancement of continuous performance task reaction time by smoking in non-deprived smokers, *Psychopharmacology* 1992;108:437-442. *See* AR (Vol. 67 Ref. 72).

Robinson JH, Pritchard WS, Davis RA, Psychopharmacological effects of smoking a cigarette with typical "tar" and carbon monoxide yields but minimal nicotine, *Psychopharmacology* 1992;108:466-472. *See* AR (Vol. 59 Ref. 236).

of RJR studies may be much higher. According to an RJR spokesperson, "[w]e've not only done research on the pharmacological effects of nicotine but we've published it in at least 250 peer-reviewed journals and symposia."[483]

RJR's sustained and sophisticated research into nicotine pharmacology demonstrates that RJR knows that (1) its product will affect consumers in a drug-like manner and (2) consumers will use its product to obtain these drug effects.

iii. RJR's Alternative Tobacco Products. Further evidence of RJR's understanding of the central role of nicotine in smoking is provided by RJR's development of alternative tobacco products that are designed to deliver nicotine, but not other constituents of cigarette smoke, to the consumer.

RJR's efforts to develop alternative nicotine delivery systems began more than 20 years ago. As noted above, Claude Teague recommended in 1972 that RJR develop "some simpler, 'cleaner', more efficient and direct way to *provide the desired nicotine dosage* than the present system involving combustion of tobacco."[484] In recent years, RJR has developed at least two alternative tobacco products.

Smith KM, Mitchell SN, Joseph MH, Effects of chronic and subchronic nicotine on tyrosine hydroxylase activity in noradrenergic and dopaminergic neurones in the rat brain, *J Neurochem* 1991;57(5):1750-1756. *See* AR (Vol. 60 Ref. 266).

Wonnacott S, Drasdo AL, Presynaptic actions of nicotine in the CNS, in *Effects of Nicotine on Biological Systems,* eds. Adlkofer F, Thurau K (1991), at 295-305. *See* AR (Vol. 62 Ref. 302).

[483] Collins G, Legal attack on tobacco intensifies, *New York Times,* Jun. 9, 1995. *See* AR (Vol. 21 Ref. 240a).

[484] Teague CE (R.J. Reynolds Tobacco Co.), *Research Planning Memorandum on the Nature of the Tobacco Business and the Crucial Role of Nicotine Therein* (Apr. 14, 1972), at 7 (emphasis added). *See* AR (Vol. 531 Ref. 125).

First, in the late 1980's, RJR developed and briefly marketed Premier, a product that worked by heating nicotine and glycerol-coated aluminum beads contained in an aluminum cylinder rather than by burning tobacco. Premier resembled a conventional cigarette in appearance only. Inside, it contained a carbon tip, which served as the heat source for the aluminum cylinder.[485] RJR documents show that RJR was acutely interested in Premier's ability to deliver nicotine to the smoker's blood and brain. For instance, RJR conducted extensive plasma studies to show that smokers using Premier would achieve approximately the same level of nicotine in their blood as smokers using conventional cigarettes.[486] Other smoke components, however, were reduced by about 90%.[487] Premier functioned like the alternative nicotine delivery system recommended by Teague. Indeed, RJR used Teague's terminology to market Premier, advertising the product as a "cleaner" cigarette.[488]

More recently, RJR has begun test-marketing a low-smoke product called Eclipse.[489] Like Premier, Eclipse relies on a carbon tip as a heat source. The tip heats a

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[485] *Chemical and Biological Studies on New Cigarette Prototypes that Heat Instead of Burn Tobacco* (Winston-Salem NC: R.J. Reynolds Tobacco Co., 1988), at 1-10. *See* AR (Vol. 107 Ref. 980).

[486] *Id.* at vii, 457-458, 479-483, 490-492.

deBethizy JD, Borgerding MF, Doolittle DJ, *et al.* (R.J. Reynolds), Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco, *J. Clin. Pharmacol.*, 1990;30:755-763. *See* AR (Vol. 47 Ref. 78).

[487] *Id.* at 757.

[488] Pollay RW, Carter-Whitney D, *More Chronological Notes on the Promotion of Cigarettes* (History of Advertising Archives, Aug. 1990), at 29. *See* AR (Vol. 215 Ref. 2891).

[489] Cabell B, Smokeless cigarette makers hope to Eclipse market, Live Report (Jun. 3, 1996). *See* AR (Vol. 711 Ref. 11).

Jones C, Reynolds not blowing smoke when it comes to keeping a lid on Eclipse, *The Richmond Times Dispatch* (Jun. 10, 1996). *See* AR (Vol. 711 Ref. 12).